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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/858,087	05/16/97	HARRISON	

HM12/021

EXAMINER
FORTNER

ART UNIT
1641

PAPER NUMBER

02/19/98

DATE MAILED:

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Office communication concerning this application or
proceeding, and be advised of the action taken on such communication.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/858,087	Harrison
Examiner Porter	Group Art Unit 1641

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

Responsive to communication(s) filed on 11-25-98 + 11-17-98.

This action is FINAL.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

Claim(s) 16-31 + 35-39 is/are pending in the application.

Of the above claim(s) 17, 19-21, 27-31, 35-39 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 14, 18, 22, 23-26 is/are rejected.

Claim(s) _____ is/are objected to.

Claim(s) _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The proposed drawing correction, filed on _____ is approved disapproved.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

Information Disclosure Statement(s), PTO-1449, Paper No(s). 9 Interview Summary, PTO-413

Notice of Reference(s) Cited, PTO-892 Notice of Informal Patent Application, PTO-152

Notice of Draftsperson's Patent Drawing Review, PTO-948 Other _____

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DETAILED ACTION

Claims 1-15, 32-34 have been canceled; new claims 35-39 have been added; claims 16-31 and 35-39 are pending.

Election/Restriction

1. Applicant's election without traverse of claims 16-31 and species number 5, specifically claim 22, drawn to a method of detecting candidate compounds which are inhibitors of lymphocytes in Paper No. 8 is acknowledged. Claims 16, 18, 23-26 are considered to be generic claims.
2. Newly submitted claims 35-39 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 35, 36 and 37 depend from claim 17 which is drawn to a non-elected species; Claim 39 finds support in the specification and in claim 14, which is drawn to a non-elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 35-39 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. With respect to paragraphs 8 and 9 of the Office action in paper number 6, the examiner acknowledges that these paragraphs do not apply to instantly claimed inventions and are hereby withdrawn.

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4.

Drawings

5. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Page 8, line 12 recites "6" but figure 1 shows 6 and 6'; correction is requested.

Information Disclosure Statement

6. The information disclosure statement has been considered as to the merits prior to first action.

7.

Specification

8. The attempt to incorporate subject matter into this application by reference to various journal articles on page 1 is improper because the incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins , 486 F. 2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins , 486 F. 2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins , 486 F. 2d 577, 179 USPQ 167 (CCPA 1973).

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9. The use of the trademark Fluo-3, Pluronic Fura, PCRD2, Aquasil have been noted in this application (pages 28, line 15 and 23; page 18, lines 1-5 and 29; page 21, line 20. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

10. The disclosure is objected to because of the following informalities: the use of abbreviations in the specification is permitted upon initial definition of the term; clarification of the terms: MSE, SNAFL, SNARF, HSG-IMT; VAMP; Pt; COPI is requested (page 22, line 28, page 18, lines 2-3, page 23, line, 9; page 21, line 19.

11. ***Claim Rejections - 35 U.S.C. § 112***

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 16, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 16 recites the phrase "capable of flowing"; recitation of positively stated limitations define patentable weight; "capable of" does not a positive limitation but only requires the ability to so perform. *In re Hutchison*, 69 USPQ 138.

Claim 22 is pendent upon a non-elected claim and is therefore indefinite.

Claim Rejections - 35 U.S.C. § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 16, 18, 22, and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okun et al (US Pat. 5,804,436) taken with Tracey or Wilding et al references of record on 1449).

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Okun et al disclose an apparatus and method of real time measurement of cellular response, wherein the cellular response of a test compound or series of test compounds of a flowing suspension of living cells is combined with a concentration of a test compound and directed through a detection zone and a cellular response of the living cells is measured. The reference teaches the evaluation of antagonists on a living cell population, wherein a standard compound is an agonist and an alteration of the known effect detected is indicative of the test compound is an antagonist of the known effect (col. 5, lines 13-24 and 58-67 through col. 6, lines 1-41). The use of positive and negative pressure systems are disclosed (col. 14, lines 25-33), the use of a cell mixing chamber is disclosed (col. 12, lines 25-34) a detection zone which provides for flow through analysis or with time delay analysis which takes into consideration the incubation period of the cell compound interaction (col 13, lines 39-61), as well as stop and start signals (col. 14, lines 61). The device may utilize capillary sized flow components (col. 13, lines 20-30), miniature solenoid type valves, provides for diverting valves for alternating the supply of either cells, buffer, compound or standard (col. 16, lines 26-52). Okun discloses cells for use in the disclosed apparatus and method, wherein the type of cell used is chosen based on the type of effect and receptor being evaluated, wherein T-Cells are taught (col. 28, line 7). The reference claims an apparatus for automatically measuring the effect of a plurality of test compounds on living cells which utilizes a conduit which establishes a flow channel, a mixing chamber, a detector, the use of intracellular dye, computer analysis of data and control of the apparatus, as well as first, second, third and fourth flow channels (see claim 1-50).

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Okun et al clearly teaches the evaluation of antagonists on living cells in a flowing system at the capillary level, and therefore show a microfluidic device which may use either negative or positive pressure sources for the evaluation of an effect on a cell population and specifically suggests the use of T-cell, a known subclass of lymphocytes, and the detection zone may be one in which flow is continuous or delayed depending on the effect to be observed but differs from the instantly claimed invention by failing to specifically show the use of a micro machined device which comprises flow channels.

Tracey et al disclose micro machined devices in an analogous art for the purpose of showing devices which may be used in blood cell studies, and specifically shows the use of red blood cells and suggests the extension of the technology to leukocyte (lymphocytes are a subset of leukocytes) cell analysis. Wilding shows the use of channels micro machined in an analogous art for the purpose of defining means and methods for the analysis of blood cells, to include white blood cells in channels which have been coated with a protein solution comprising albumin (page 44, col. 2, paragraph 2) .

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Okun et al with the micro machined microfluidic device of Tracey or Wilding because Tracey and Wilding both teach that the micro machine microfluidic devices provide for higher cell throughput (Tracey, page 759, col. 1, Current research section) which provides for increased sample analysis and provide for relative ease of fluid handling (Wilding, page 46, col. 2, paragraph 3), provide for nanoliter and picoliter volumes

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of samples to be evaluated, wherein the devices are inexpensive to produce and provide disposable diagnostic devices for medical applications, as well as provide a means for evaluation of experimental analogs in transport studies in complex networks and interconnected pores and provide a versatile alternative to other modes of experimentation. Therefore, the person of ordinary skill in the art would have been motivated and would have had a reasonable expectation of evaluating lymphocyte responses to potential inhibitors because Okun et al define experimental designs for ease of interpreting the effect of a chemical as an antagonist or an agonist with respect to measured parameters such as fluorescence and teach that flowing systems provide for improved sample evaluation and both Tracey and Wilding disclose flowing sample systems which evaluated samples comprising cells, and Tracey suggests the use of the system to evaluate leukocyte responses and Wilding shows the system using white blood cells in a channel which was coated with albumin and both Tracey and Wilding teach advantages to using micro machined surfaces over other microfluidic devices because sample size may be small and the through put higher than other microchip system. Therefore, in the absence of a showing of unexpected results, Okun taken with Tracey or Wilding obviate the now claimed invention of evaluating inhibitors of lymphocytes in the presence of a cell activator and a candidate compound.

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Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
18. **Nemeth et al (US Pat. 5,858,684)** is cited to show a method of screening calcium receptor active molecules which may mimic or block an effect of an extracellular ion.
19. **Ramsey (WO 96/04547)** is cited to show an apparatus and method for performing microfluidic manipulations of chemical analysis
20. **Fay et al (US Pat. 5,149,972)** is cited to show the use of a two excitation wavelength video imaging microscope together with microchannel plate technology (col. 13, lines 28-30) and discloses the use of this system for the evaluation of calcium concentration in white blood cells (col. 28, lines 9-15).
21. **Tedder et al (US Pat. 4,987,084)** is cited to show the evaluation of agonists and antagonists on B lymphocytes cell surface proteins, wherein the cytosolic calcium concentration is evaluated through flow cytometry.
22. **Singhvi et al (US Pat. 5,776,748)** is cited to show a method and apparatus for the evaluation of cellular responses to biological materials, wherein the device may comprise more than one cell type to include white blood cells and red blood cells and may function as a biosensor
23. **Weinreb et al (US Pat. 5,506,141 or 5,310,674 or 4,729,949)** is cited to show an apparatus and means of use for the evaluation of lymphocytes, wherein the apparatus comprises an inflow

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and an outflow tube, a detection zone and waste tube and affords holing of living cells and reagents necessary for the maintenance of life until such time the evaluation is complete.

24. **Parce et al (US Pat. 5,496,697)** is cited to show a micro flow chamber which is used in a method of detecting the effects of an agent on living cells, wherein the device may stop periodically for the determination of an effect.

25. **Lynggaard et al (WO 95/27210)** is cited to show an analysis method in which several fluid samples are passed in succession through a reaction channel to a detector for the reduced consumption of chemicals.

26.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

February 11,1999


JAMES C. HOUSEL 2/16/99
SUPERVISORY PATENT EXAMINER